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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,926	12/31/2001	Yocheved Hagay	10793/50	9603

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NEW YORK, NY 10004

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,926	HAGAY ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/6/02; 1/27/03;* 4/26/04; 6/7/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group V in the reply filed on 9/3/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-20 and 22-41 have been cancelled in the Paper filed 9/3/2004.

3. Claim 21 is pending and under examination.

Sequence Requirements

4. In order to have compact prosecution a first office action can be performed on this application, however, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Although the claims in the instant application are not drawn to specific sequences, the disclosure contains sequences that require SEQ ID numbers at pages 30-31, 45-46, 64, 86-87 and 91-96. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance.

5. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

6. APPLICANT IS GIVEN THE TIME ALLOTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The oath or declaration has changes to the address of inventor Orly Lifshitz that are non-initialed and non-dated

Specification

8. The abstract of the disclosure is objected to because the abstract exceeds 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

Correction is required. See MPEP § 608.01(b).

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 21 is indefinite for reciting "enhanced binding characteristics" because the antibodies "enhanced binding characteristics" are not known. This language is vague and indefinite since it encompasses antibodies having many different amino acid sequences as well as many different forms and modifications and it is not clear from the disclosure which particular "enhanced binding characteristics" are being referred to. There is insufficient information and guidance concerning the metes and bounds of said "enhanced binding characteristics" as it relates to the structure/function of the claimed antibodies. The metes and bounds of said "enhanced binding characteristics" have not been clearly defined in the specification as filed. Further, binding selectively and/or specifically to a target cell in favor of other cells can occur if the target antigen is

expressed on the target cells and not expressed on other cells. Thus, the "enhanced binding characteristics" are not defined by the claims.

b. Claim 21 recites the limitation "the CDR3". There is insufficient antecedent basis for this limitation in the claim. Claim 21 does not mention any CDR3 prior to the phrase "the CDR3".

c. Claim 21 is indefinite for reciting "first hypervariable region". Is the first hypervariable region CDR3 or is some other CDR the "first hypervariable region"? Also, are the first, second and third hypervariable regions (i.e., CDR3, CDR2 and CDR1) from the light chain or the heavy chain or are combinations of heavy and light chain CDRs contemplated? For example, are CDR1 and CDR2 from the heavy chain and CDR3 from the light chain? The claims do not state whether or not CDR3, CDR2 and CDR1 (i.e., SEQ ID NOS:8, 115 and 114, respectively) are from the heavy chain or from the light chain.

d. Claim 21 is indefinite for reciting "a construct thereof" and "a construct of a fragment". Because the phrases "a construct thereof" and "a construct of a fragment" implicitly mean a nucleic acid molecule, which encodes the claimed peptide or polypeptide comprising an Fv molecule, it is unclear what is contemplated by the phrases "a construct thereof" and "a construct of a fragment"? Does the peptide or polypeptide comprise "a construct thereof" or "a construct of a fragment"?

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a scFv and dsFv wherein the variable heavy chain comprises CDR3, CDR2, CDR1 having SEQ ID NOS:8, 115, 114, respectively, and wherein the scFv and dsFv binds glycocalicin, does not reasonably provide enablement for a scFv and dsFv wherein the variable heavy chain comprises CDR3, CDR2, CDR1 having SEQ ID NOS:8, 115, 114, respectively, and binds just any antigen or a scFv and dsFv wherein the variable light chain comprises CDR3, CDR2, CDR1 having SEQ ID NOS:8, 115, 114, respectively, or fragments of a scFv and dsFv. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claim 21 is broadly drawn to a scFv and a dsFv comprising CDR3, CDR2, CDR1 having SEQ ID NOS:8, 115, 114, respectively. Thus, the claims are drawn to a scFv or

a dsFv wherein CDR3, CDR2 and CDR1 are from a heavy and/or light chain (e.g. CDR3 and CDR1 from the heavy chain, while CDR2 is from the light chain). The claims do not state that CDR3, CDR2 and CDR1 are from the heavy chain. The claims also encompass fragments of a scFv and a dsFv that do not contain a full set of 6 CDRs, and do not bind antigen.

The specification discloses only a Y1 heavy chain comprising CDR3, CDR2 and CDR1 having SEQ ID NOS:8, 115, 114, respectively, and binds glycocalicin expressed by target cells (see "The ORF of Y1-IgG-HC" at pages 94-95 and pages 89-91). The specification does not teach an Fv molecule comprising CDR3, CDR2 and CDR1 (SEQ ID NOS:8, 115, 114, respectively) that binds an antigen other than glycocalicin. The specification does not teach an Fv molecule comprising CDR3, CDR2 and CDR1 (SEQ ID NOS:8, 115, 114, respectively), wherein said CDRs are from the heavy chain and/or light chain (e.g. CDR3 and CDR1 from the heavy chain, while CDR2 is from the light chain). Further the specification does not teach fragments of an Fv, which do not contain a full set of 6 CDRs from the heavy and light chains and would not bind antigen.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs

are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). It is unlikely that fragments of a scFv or a dsFv as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing a scFv and a dsFv fragment containing fewer than 6 CDRs, resulting in a scFv and a dsFv fragment that retains the antigen specificity of the Y1 antibody. Additionally, Applicant has provided insufficient guidance or direction to assist the skilled artisan in using a scFv and dsFv that comprises CDR3 (SEQ ID NO:8), CDR2 (SEQ ID NO:115) and CDR1 (SEQ ID NO:114) and binds to just any target cell. Further, a fragment of an Fv can be any one of the CDRs, or small amino acid sequences or even a single amino acid, which are incomplete variable regions of an antibody and lack the full complement of CDRs in their proper order and in the context of framework sequences, and would not have the required conformation for antigen-binding function. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a scFv and dsFv or fragment thereof, wherein the scFv and dsFv comprise CDR3, CDR2, CDR1 having SEQ ID NOS:8, 115, 114, respectively, and wherein the scFv and dsFv binds just any target cell. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claim 21 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 29 of copending Application No. 10/029,988. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim is drawn to a peptide or polypeptide comprising an Fv molecule having enhanced binding characteristics so

as to bind selectively or specifically to a target cell in favor of other cells, wherein the binding selectivity or specificity is primarily determined by a first hypervariable region and wherein the Fv is a scFv or a dsFv and optionally having one or more tags and wherein the binding selectivity or specificity is secondarily influenced by a second hypervariable region, by a third hypervariable region, and/or by one or more of the upstream or downstream regions flanking the first, the second and/or the third hypervariable regions and wherein the second and third hypervariable regions are a CDR2 and CDR1 hypervariable region, respectively, and wherein the CDR3, CDR2 and CDR1 regions have the amino acid sequences SEQ ID NOS:8, 115 and 114, respectively, and claim 29 of copending Application No. 10/029,988 is drawn to an antibody multimer comprising SEQ ID NOS:8, 115, and 114. SEQ ID NOS:8, 115 and 114 are identical to SEQ ID NOS:8, 115 and 114 instantly claimed. Thus, as a property is inherent to a product, the antibody multimer comprising SEQ ID NOS:8, 115 and 114 would inherently contain the enhanced binding characteristics as instantly claimed. The antibody multimer comprising SEQ ID NOS:8, 115, and 114 of copending Application No. 10/029,988 reads on instant claim 21 because "comprising" as recited in instant claim 21 is open language meaning that the instantly claimed peptide or polypeptide "comprising" an Fv encompasses an antibody multimer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

Application No. 10/029,926

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE